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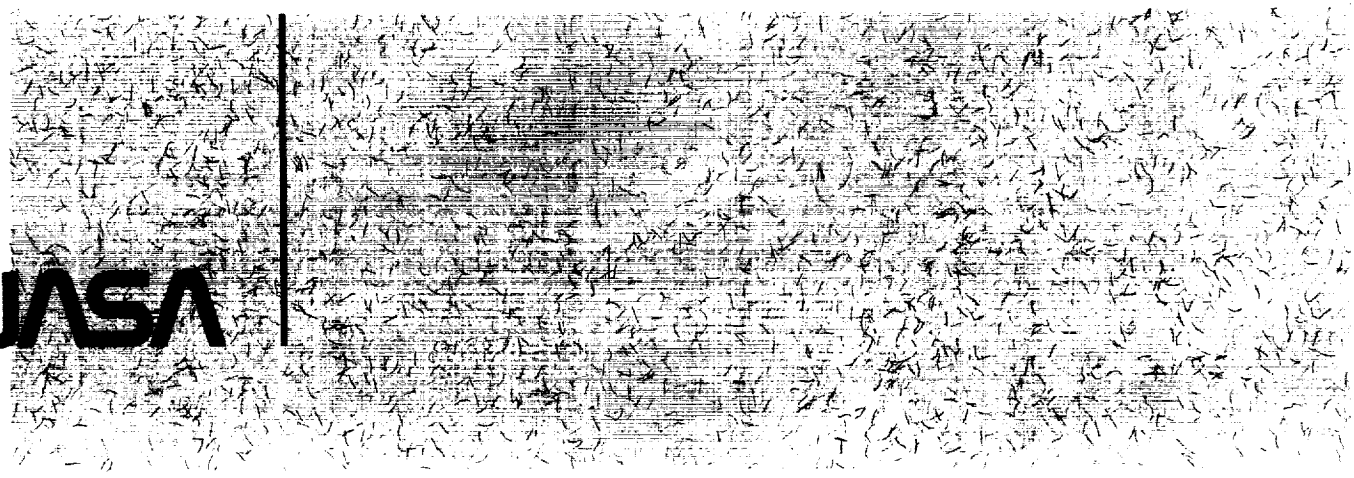

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Francis A. Cucinotta,
and Judy L. Shinn
Langley Research Center
Hampton, Virginia

National Aeronautics and Space Administration
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Abstract

A multilesion cell kinetic model is derived, and radiation kinetic coefficients are related to the Katz track structure model. The repair-related coefficients are determined from the delayed plating experiments of Yang et al. for the C3H10T½ cell system. The model agrees well with the X-ray and heavy ion experiments of Yang et al. for the immediate plating, delayed plating, and fractionated exposure protocols employed by Yang. A study is made of the effects of target fragments in energetic proton exposures and of the repair-deficient target-fragment-induced lesions.

Introduction

Estimates of space radiation risk are largely based on biological response data obtained at high dose rates. Extrapolation to the low level continuous exposures in space requires a knowledge of repair processes. This report is an attempt to model those repair processes for a simple cell system and to understand some of the factors that are important for space exposure.

Living cells are found to proceed through a series of events leading to cell division referred to as the cell cycle. There are two significant events, denoted by S phase (synthesis of DNA material) and M phase (mitosis). These phases are separated by two gaps called G_1 (following M) and G_2 (following S and preceding M). The gaps are known to be active metabolic periods linked to repair processes (Mitchison 1971). The cell cycle may be limited by the physical/chemical environment, interaction with adjacent cells, or availability of nutrients. Indeed, the growth of specialized tissues in complex organisms is controlled by cell contact interaction and exchange of growth-controlling chemical compounds (Allen 1962).

The role of repair in radiobiological response was elegantly presented by Fritz-Niggli (1988). The M phase appears accident prone, and G_1 is instrumental in making repairs. Evidence of these facts lies in the following observations. First, the errors of the S and M phases are normally repaired, otherwise life would not exist (Fritz-Niggli 1988). Second, radiation injury sustained in the M phase of mouse cells is more likely to end cell propagation than injury received in the G_1 and G_2 phases (Sinclair 1968). The cell cycle progression can be blocked (delayed) in G_1 or G_2 by injury sustained in that phase until the injury is repaired (Mitchison 1971). These simple facts alone provide insight as to the biological response of more complex organisms.

A tissue sample from a complex organism exhibits a distribution of cells over various phases. The highly differentiated tissues are predominantly G_1 and are well-known to be radiation resistant. Stem cell tissues have significant populations of M- and especially S-phase cells and are in part responsible for acute radiation syndrome in higher animals. Immature individuals are more sensitive than adults, and the embryo is most sensitive of all. Clearly, a viable model of radiation response must account for the varying repair kinetics for the differing cell phases and the distribution of tissue cells within the cell cycle.

In a previous report (Wilson and Cucinotta 1991), we presented a simple phase-dependent repair model in which track structure effects were added through the use of the Katz et al. (1971) formalism. Repair coefficients were estimated from the experiments of Yang et al. (1989) on stationary G_1 mouse cells in which varying amounts of repair in G_1 phase were allowed before cell cycling. Highly efficient repair was demonstrated for G_1 phase for light ions, while high energy ^{56}Fe exposures showed little repair, which is in good agreement with the kinetic model.

In the present report, we develop a more comprehensive model of the cell kinetics. We still rely on the Katz model for a description of the physics of the track structure. The cell kinetics are represented by an unbounded set of coupled linear differential equations describing multiples of lesions within the cell. The kinetic coefficients in the model are to be determined from repair-dependent cell response data.

Radiation Injury and Repair

Varied and complicated events can occur within a cell and terminate the cell progression. In distinction, a few events at specific loci with minimal additional damage are required in order that the cell can express other biological end points in subsequent generations. Consequently, specific mechanisms may one day be specified for many biological end points, but cell death for which thousands of mechanisms are likely involved will be limited to phenomenological analysis. For the moment, we will consider the kinetics related to cell death, while events related to other biological end points appear here simply as survivors. We are likewise interested in low dose effects for which enzyme inactivation and membrane damage are negligible. We concern ourselves with lesions which presumably affect the DNA material as the main source of cell injury. It seems clear to us that the nascent lesions result from the formation of free radicals within the cell and that a large number of chemical bonds could be broken. Indeed, many such lesions could accumulate within a given cell. The

present model considers explicitly only those lesions that can ultimately result in cell death. A coupled set of first-order linear differential equations are assumed to govern the time development of cellular populations n_i, having received a number i of radiation-induced lesions. The initial cell population $n_0(0)$ having no lesions is subject to radiation-induced lesions at a rate k_i. The rate k_i scales linearly with the flux of ionizing radiation and depends on particle type, α_i is the lesion repair rate, and the number of i-fold lesions repaired per unit time is $\alpha_i n_i$. The rate α_i is composed of repair (α_{r_i}) and misrepair (α_{m_i}) rates for the lesion to be restored or permanently injured. The equations within a given cell phase are taken as the gains and losses through repair and injury, respectively, as given by

$$\dot{n}_0 = \sum_{i=1}^{\infty} \alpha_{r_i}\, n_i - k\, n_0 \tag{1}$$

$$\dot{n}_i = \sum_{j=0}^{i-1} k_{i-j}\, n_j - k\, n_i - \alpha_i\, n_i \tag{2}$$

where the subscript of n_i denotes the multiplicity of (chemical) lesions. We allow for misrepair in the model by the time evolution equation for misrepaired cell population n_d as

$$\dot{n}_d = \sum_{i=1}^{\infty} \alpha_{m_i}\, n_i \tag{3}$$

Misrepair in our sense is permanent structural changes in the nuclear material that lead to cell death. Conservation of cell number dictates $\alpha_i = \alpha_{r_i} + \alpha_{m_i}$ and $k = k_1 + k_2 + \ldots$ within a given cell phase. The reaction rate coefficients k_i are in units of s^{-1}. They are related to radiation-induced lesions within the nucleus (presumably chromosomes) and are proportional to particle flux (primary ions or secondary charged products). Below we utilize the track structure model (Katz et al. 1971) to estimate these rates. In equations (1)–(3), we have assumed the rates k_i are independent of possible previous lesions; however, this restriction could be lifted if necessary. The lesions are chemically active species neutralized by enzyme activity at rate constants α_i. This is not the most general model but will hopefully represent the essential kinetics for cell survival.

A simple solution to the above equations can be found for a high exposure rate of short duration t_r. Experimentally, repair effects are observed to occur on time scales of many seconds (Curtis 1986). For an impulsive exposure (short duration), we then neglect the repair terms in equations (1) and (2) and find

$$n_0(t_r) = n_0(0)\; e^{-kt_r} \tag{4}$$

where $n_0(0)$ is the initial population. Solutions for successive terms of equation (2) are found for the nascent populations as

$$n_1(t_r) = n_0(0)\; k_1\, t_r\, e^{-kt_r} \tag{5}$$

$$n_2(t_r) = n_0(0)\; k_2\, t_r\, e^{-kt_r} + \frac{1}{2}\, n_0(0)\; (k_1\, t_r)^2\; e^{-kt_r} \tag{6}$$

$$n_3(t_r) = n_0(0)\; k_3\, t_r\, e^{-kt_r} + \frac{2}{2!}\, n_0(0)\; k_1\, k_2\, t_r^2\, e^{-kt_r} + \frac{1}{3!}\, n_0(0)\; (k_1\, t_r)^3\; e^{-kt_r} \tag{7}$$

where high-order terms are of similar form. At time t following exposure, the repair processes result in

$$n_0(t) = n_0(t_r) + \sum_{i=1}^{\infty} \frac{\alpha_{r_i}}{\alpha_i}\, n_i(t_r) \left(1 - e^{-\alpha_i t}\right) \tag{8}$$

which is a direct generalization of our earlier result (Wilson and Cucinotta 1991). Similarly, the multi-lesion densities are given as

$$n_i(t) = n_i(t_r)\; e^{-\alpha_i t} \tag{9}$$

with a total misrepair density as

$$n_d(t) = \sum_{i=1}^{\infty} \frac{\alpha_{m_i}}{\alpha_i}\, n_i(t_r)\; \left(1 - e^{-\alpha_i t}\right) \tag{10}$$

The model described in equations (1)–(10) contains many unknown coefficients. Of particular note is the importance of lesions where $i \gg 1$ in describing survival curves. To be of practical use, only a small number of terms should be of importance. We now consider the track structure model of Katz et al. (1971), from which we will find a useful reduction of the linear kinetic model.

Katz Model

The cellular track model of Katz et al. (1971) and Katz (1988) attributes biological damage from energetic ions to the secondary electrons (delta rays) produced along the path of the ion. The effects caused by energetic ions are correlated with those of gamma rays by assuming that the response in sensitive sites near the path of the ion is part of a larger system irradiated with gamma rays at the same dose. The response due to ion effects is then determined by

knowledge of the gamma-ray response and the delta-ray dose surrounding the path of the ion. For a multi-target response with target number m, the inactivation of cells by gamma rays is assumed to follow a Poisson distribution reflecting the random accumulation of sublethal damage, with a radiosensitivity parameter D_o.

For the inactivation of cells by ions, two modes are identified: "ion kill," which corresponds to intra-track effects and "gamma kill," which corresponds to intertrack effects. Here, the ion-kill mode is unique to ions corresponding to single-particle inactivation of cells described by the cross section σ. The inactivation cross section for a sensitive site whose response to radiation is ahistoric is determined as (Katz et al. 1971)

$$\sigma = \int_0^\infty 2\pi r\, dr \left(1 - e^{-\overline{D}/D_o}\right)^m \tag{11}$$

where $\overline{D}$ is the average dose at the sensitive site at a distance r from the ion track. The evaluation of the cross section is separated by Katz et al. (1971) into a so-called grain-count regime, where inactivation occurs randomly along the path of the particle, and into the so-called track-width regime, where many inactivations occur and are said to be distributed like a "hairy rope." In the grain-count regime, σ may be parameterized as

$$\sigma = \sigma_o \left(1 - e^{-Z^{*2}/\kappa\beta^2}\right)^m \tag{12}$$

where σ_o is the plateau value of the cross section, β is the ion velocity in units of velocity of light, the effective charge number is given by

$$Z^* = Z\left(1 - e^{-125\beta/Z^{2/3}}\right) \tag{13}$$

and κ is a parameter related to the radius a_o of the sensitive site by

$$D_o\, a_o^2/\kappa \approx 2 \times 10^{-7}\ \text{erg/cm} \tag{14}$$

The transition from the grain-count regime to the track-width regime is observed (Katz 1988) to take place at a value of $Z^{*2}/(\kappa\beta^2)$ on the order of 4. The grain-count regime is at the lower values of $Z^{*2}/(\kappa\beta^2)$ and the track-width regime at higher values.

The fraction of cells damaged in the ion-kill mode is $P = \sigma/\sigma_o$; note that in the track-width regime $\sigma > \sigma_o$, and it is assumed that $P = 1$. The track model assumes that a fraction of the ion's dose $(1 - P)$ acts cumulatively with that of other particles to inactivate cells in the gamma-kill mode. The surviving fraction of a cellular population $n_0(0)$, whose response parameters are m, D_o, and κ or a_o after irradiation by a fluence of particles F, is then written as

$$\frac{n_0(\infty)}{n_0(0)} = \pi_i \times \pi_\gamma \tag{15}$$

where the ion-kill survival probability π_i is

$$\pi_i = e^{-\sigma F} \tag{16}$$

and the gamma-kill survival probability is

$$\pi_\gamma = 1 - \left(1 - e^{-D_\gamma/D_o}\right)^m \tag{17}$$

The gamma-kill dose fraction is

$$D_\gamma = (1 - P)D \tag{18}$$

where D is the absorbed dose. Here, within the context of our analysis, the Katz response parameters for the surviving cellular populations that are (infinitely) delayed for plating $n_0(\infty)$ are considered.

The relative biological effectiveness (RBE) at a specific survival level is given by

$$\text{RBE} = D_x/D \tag{19}$$

where

$$D_x = -D_o \ln\left\{1 - \left[1 - \frac{n_0(\infty)}{n_0(0)}\right]^{1/m}\right\} \tag{20}$$

is the X-ray dose at which this level is obtained. Equations (11) through (20) represent the cellular track model for monoenergetic particles. We must now consider the relationship of the kinetic model to the Katz model.

Physics and Kinetics of Cell Injury

The Katz model is formulated on the basis of physical arguments about track structure, geometric arrangement of sensitive (chemical bond) sites, size of the cell nucleus, and energy thresholds for changes in the cell molecules. In practice, the Katz parameters (m, D_o, σ_o, and κ) are determined from biological experiments for a given cell system and experimental protocol. The degree to which cell repair is reflected in the final parameters is uncertain, but the effects of different experimental protocols on the Katz parameters are well-known and in some way reflect repair mechanisms. We will attempt to better define the relationship of repair to the Katz model parameters within the context of the present repair kinetic model.

In the Katz model, it is assumed that electromagnetic radiations form single lesions with an efficiency related to D_o and that generally more than one lesion ($m \geq 2$) is required to express the biological effect (cell death in the present study). We assume that cells in the G_1 phase show complete repair of lesion multiples of less than m. If the cells are irradiated with gamma rays in G_1 and are held in this phase until repair is complete, then the surviving population is found to be

$$n_0(\infty) = n_0(t_r) + \sum_{i=1}^{m-1} n_i(t_r) \tag{21}$$

assuming maximum repair in G_1 (i.e., $\alpha_{r_i}/\alpha_i = 1$ for $i < m$). Equation (21) allows us to relate the k_i coefficients to the corresponding Katz parameters of equations (11) to (18) as applied to the appropriate experimental protocol (namely, G_1 exposure followed by complete G_1 repair). In the kinetic model, $n_0(0)$ is the initial number of G_1 cells, and equation (21) is rewritten as

$$\frac{n_0(\infty)}{n_0(0)} = e^{-kt_r} + \sum_{i=1}^{m} k_i t_r e^{-kt_r} + \frac{2}{2!} k_1 t_r \sum_{i=1}^{m-1} k_i t_r e^{-kt_r} + \frac{1}{3!}(k_1 t_r)^2 \sum_{i=1}^{m-2} k_i t_r e^{-kt_r} + \ldots \tag{22}$$

According to the Katz model, a system with $m = 3$ has a gamma-ray response given by

$$\frac{n_0(\infty)}{n_0(0)} \approx 1 - \left(1 - e^{-D_\gamma/D_o}\right)^3 \approx 1 - \left(\frac{D_\gamma}{D_o}\right)^3 \tag{23}$$

which is matched to equation (22) by taking a Taylor series expansion for the gamma-kill mode ($\pi_i = 1$) resulting in

$$k_1 t_r \approx 6^{\frac{1}{3}} \; D_\gamma/D_o \tag{24}$$

$$k_m t_r \approx 0 \qquad (m > 1) \tag{25}$$

as is appropriate for gamma rays. Similarly, the remaining Taylor series terms in equation (22) can be determined for the ion-kill mode ($\pi_\gamma = 1$) from the remaining Katz terms by noting that for strictly ion-kill kinetics

$$k_3 t_r \approx \sigma F \tag{26}$$

$$k_2 t_r \approx 0 \tag{27}$$

Although k_i may reflect both physical and chemical processes because of their empirical nature, we assume here that they are most clearly identified with the physical processes discussed by Katz. We now examine means by which repair rates can be estimated, at least for some experimental cell systems.

Three-Target Repair/Misrepair Systems

The above can be applied to an approximate three-target system as

$$\frac{n_0(\infty)}{n_0(0)} \cong \left[1 + \frac{\alpha_{r_1}}{\alpha_1} 6^{\frac{1}{3}} \frac{D_\gamma}{D_o} + \frac{\alpha_{r_2}}{\alpha_2} \frac{6^{\frac{2}{3}}}{2} \frac{D_\gamma^2}{D_o^2}\right] \times e^{-\sigma F - 6^{\frac{1}{3}} \; D_\gamma/D_o} \tag{28}$$

where D_γ, D_o, and σF are related to the usual Katz model for $m = 3$, and $\frac{\alpha_{r_1}}{\alpha_1}$ and $\frac{\alpha_{r_2}}{\alpha_2}$ are the repair ratios for the once-hit and twice-hit cells. Presumably, $\frac{\alpha_{r_1}}{\alpha_1} \geq \frac{\alpha_{r_2}}{\alpha_2}$. We take

$$\frac{\alpha_{r_2}}{\alpha_2} = \left(\frac{\alpha_{r_1}}{\alpha_1}\right)^p \tag{29}$$

in the present analysis and expect p to be 2 or greater. In the limit of vanishing dose

$$\text{RBE} \approx 6^{-\frac{1}{3}} \; D_o \frac{\alpha_1 \sigma}{\alpha_{m_1} L} + 1 - \frac{\sigma}{\sigma_o} \tag{30}$$

where L is the linear energy transfer. Note that the RBE is unbounded for small α_{m_1}. The RBE in the Katz model is found to increase with ion dose as $D^{-1+1/m}$ (Cucinotta et al. 1991a; Katz and Cucinotta 1991). A similar dependence on dose is found in the present formalism at higher exposure levels than assumed in equation (30); however, misrepair prevents a one-to-one correspondence.

Application to Cell Survival in HZE Exposure

The experiments of Yang et al. (1989) utilized contact-stabilized mouse cells C3H10T½ in the G_1 phase. In one set of experiments, the cells remained in the G_1 phase for 24 hr before separation and introduction into a nutrient medium to stimulate growth (delayed plating). A second series of cells was immediately plated and thus the cell kinetics were greatly altered by entering the synthesis cycle (S phase) soon after exposure. It is well-known (Sinclair 1968) that the early G_1 phase is efficient in cell repair, while the early S phase is mistake prone (Radman et al. 1981). We assume the G_1 phase repair ratio α_{r_1}/α_1 is near maximum, while the accident-prone early S phase has a significant rate of misrepair. Furthermore, survival of the mouse cell

is shown by Katz to be a three-target system, and even higher rates of misrepair are expected from the doubly injured cell ($p \gg 2$), especially later in the cell cycle.

The Katz parameters (see table I) for the delayed experiments (Katz et al. 1971) are used directly to estimate σF, D_o, and D_γ, with the assumption that $\frac{\alpha_r}{\alpha} = 1$, and provide a good fit, as expected, to the delayed plating data of Yang et al. Good agreement is found for the immediately plated cells by taking $p = 6$ and $\alpha_{r_1}/\alpha_1 = 0.7$ (for the exponential population). The results are shown in figure 1. The figure is arranged in order of increasing linear energy transfer (LET), and the sigmoid behavior associated with multitarget phenomena is apparent for the lighter ions. The sigmoid behavior disappears at higher LET (except for the Ar data), and the repair processes become less effective as the ion-kill mechanism of Katz dominates. Good agreement is found for all the ions except Ar ions. There may be some unexplained differences in the cell batches used in the Ar ion experiments.

Table I. Katz Parameters Used in the Present Track Structure Repair/Misrepair Model

	σ_0, cm^2	κ	m	D_o, Gy
C3H10T½	5×10^{-7}	750	3	2.8

Comparisons of calculated and measured RBE values for several ions are shown in table II at survival levels of 10 percent and 50 percent for immediate plating conditions. The agreement with experiment is very good except for the U ion. Here, we have not taken track-width effects into account. The maximum RBE value given by equation (30) with $\alpha_{r_1}/\alpha_1 = 0.7$ is also shown in table II. We note that for the delayed plating experiments, no maximum RBE is predicted in the kinetic model or the Katz model.

Repair-Rate-Dependent X-Ray Experiments

Another useful experiment is to expose a stationary G_1 population and to allow G_1 phase repair to proceed for a fixed time t followed by plating in which the full cell cycle is promoted. The initially injured cell population after exposure described by $n_i(t_r)$ is given by equations (4) to (7). The G_1 repair phase is described by

$$n_0(t) = n_0(t_r) + \sum_{i=1}^{m-1} \left(\frac{\alpha_{r_i}}{\alpha_i}\right) n_i(t_r) \left(1 - e^{-\alpha_i t}\right) \quad (31)$$

and

$$n_i(t) = n_i(t_r)\, e^{-\alpha_i t} \quad (32)$$

Table II. RBE for Survival of C3H10T½ Cells (Immediate Plating)

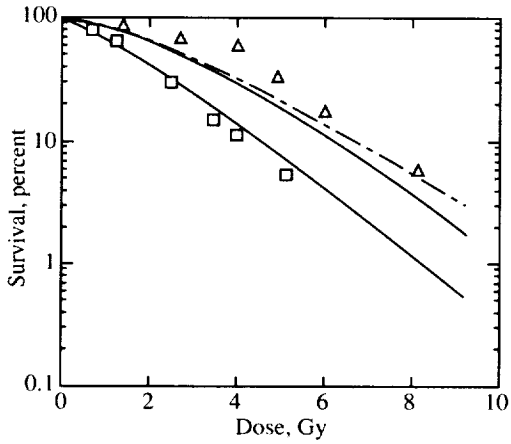
		10 percent	50 percent	Maximum
Radiation	LET*	Experiment (Theory)	Experiment (Theory)	Theory
X-rays		1.00 (1.00)	1.00 (1.00)	1.00
C-12	10	1.00 (1.03)	1.00 (1.02)	1.10
Ne-20	32	1.50 (1.29)	1.56 (1.38)	1.71
Si-28	50	1.50 (1.52)	1.67 (1.67)	2.28
Si-28	82	2.23 (2.10)	3.00 (2.51)	3.73
Ar-40	140	2.30 (2.60)	3.00 (3.15)	5.00
Fe-56	192	2.20 (2.50)	3.10 (3.08)	4.87
Fe-56	286	2.00 (2.35)	3.00 (2.99)	4.68
Fe-56	475	1.62 (1.65)	2.72 (2.11)	3.31
U-238	1860	0.88 (0.43)	1.20 (0.55)	0.86

*LET in units of keV/μm

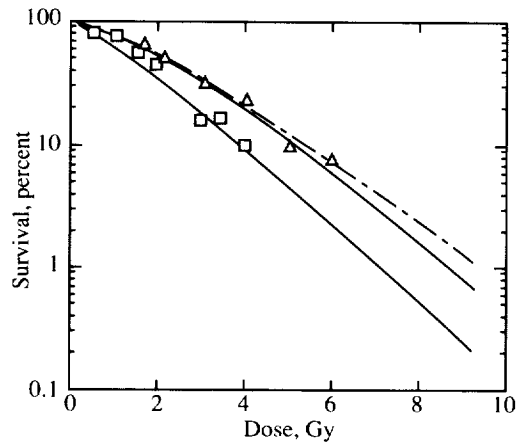
If after a time t the cells are placed into a normal cell cycle, the S-phase repair rates are quite different and the system proceeds at the repair rates found by Wilson and Cucinotta (1991) as

$$n_0(\infty) = n_0(t_r) + \sum_{i=1}^{m-1} \left(\frac{\alpha_{r_i}}{\alpha_i}\right) n_i(t_r) \left(1 - e^{-\alpha_i t}\right) + \sum_{i=1}^{m-1} \left(\frac{\alpha'_{r_i}}{\alpha'_i}\right) n_i(t_r)\, e^{-\alpha_i t} \quad (33)$$

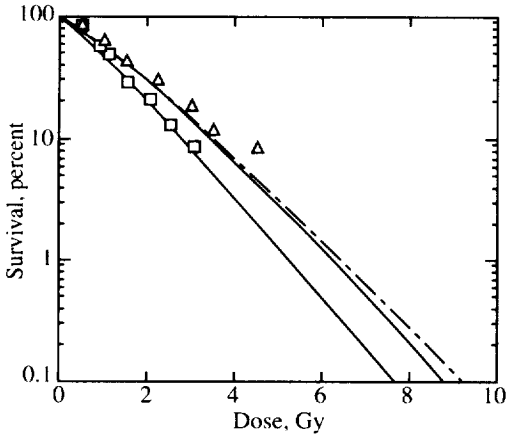
where t remains as the G_1 repair period, and α'_{r_i} and α'_i are the repair rate coefficients for an exponential



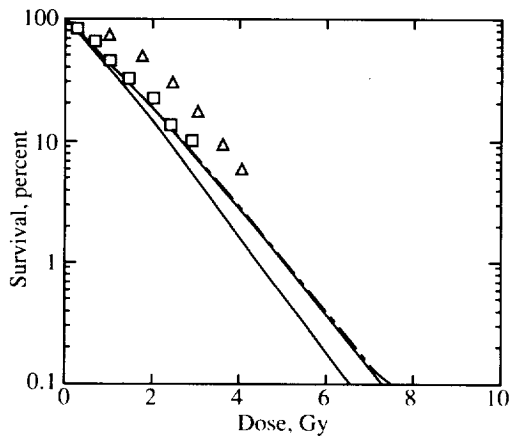
(a) ^{20}Ne; 425 MeV/amu; 32 keV/μm.



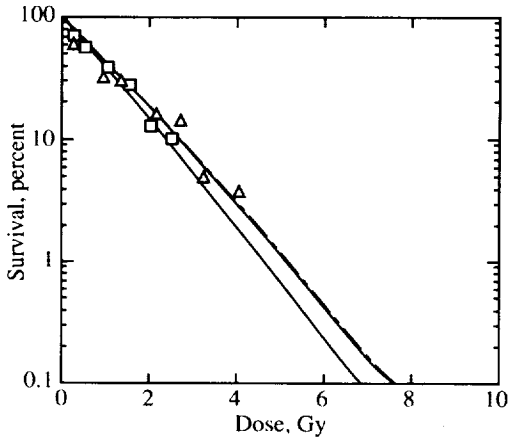
(b) ^{28}Si; 670 MeV/amu; 50 keV/μm.



(c) ^{28}Si; 320 MeV/amu; 82 keV/μm.



(d) ^{40}Ar; 330 MeV/amu; 140 keV/μm.



(e) ^{56}Fe; 600 MeV/amu; 190 keV/μm.

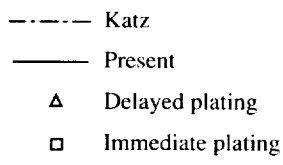


Figure 1. Cell survival of C3H10T½ for delayed plating and immediate plating.

population. Results are shown in figure 2 as a function of G_1 delay for two X-ray exposure levels of 3 and 6 Gy.

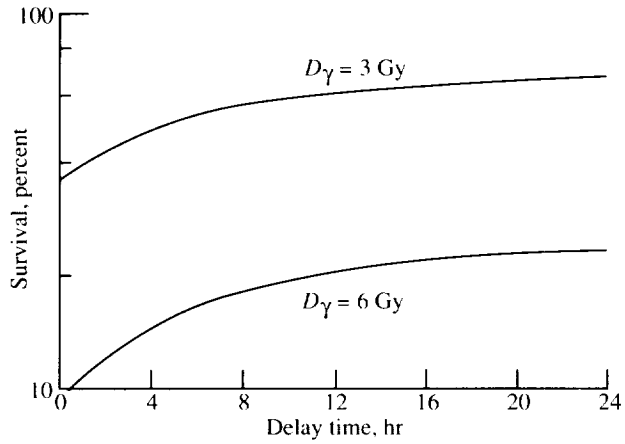


Figure 2. Percent survival at two exposure levels as a function of G_1 delay time before plating.

Another approach to study G_1 repair rates is to use fractionated exposures of a G_1 population. The initial exposure followed by a G_1 repair period of length t results in a cell population after repair of

$$n_0(t) = n_0(t_r) + \sum_{i=1}^{m-1} \left(\frac{\alpha_{r_i}}{\alpha_i}\right) n_i(t_r)\left(1 - e^{-\alpha_i t}\right) \quad (34)$$

and

$$n_i(t) = n_i(t_r) e^{-\alpha_i t} \quad (35)$$

A subsequent exposure of duration t_r results in a new population:

$$n_0'(t_r) = n_0(t)\ e^{-kt_r} \quad (36)$$

$$n_1'(t_r) = n_i(t)\ e^{-kt_r} + k_1\, t_r\, n_0(t)\ e^{-kt_r} \quad (37)$$

$$n_2'(t_r) = n_2(t)\ e^{-kt_r} + n_1(t)\ k_1\, t_r\, e^{-kt_r} + \frac{1}{2}\, n_0(t)\ k_1^2\, t_r^2\, e^{-kt_r} \quad (38)$$

which if plated immediately after exposure yields

$$n_0'(\infty) = n_0'(t_r) + \sum_{i=1}^{m-1} \left(\frac{\alpha'_{r_i}}{\alpha_i}\right) n_i'(t_r) \quad (39)$$

These results are compared with the variable repair and fractionated exposure experiments of Yang et al. (1989) in figure 3. The agreement is excellent.

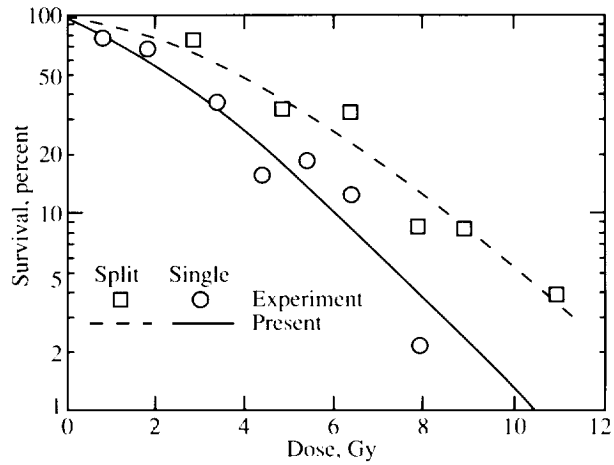


Figure 3. Cell survival for single and split exposures from 225 kV_p X-rays.

Target Fragments in Proton-Induced Kinetics

The target fragmentation fields are found in closed form in terms of the collision density (Wilson 1977) because these ions are of relatively low energy. At a location x away from any interface, the target fields ϕ_α are in a local equilibrium with the passing ion flux ϕ_j and may be written as

$$\phi_\alpha(x, E_\alpha; E_j) = \frac{1}{S_\alpha(E_\alpha)} \int_{E_\alpha}^{\infty} \frac{d\Sigma_{\alpha j}(E', E_j)}{dE'} \phi_j(x, E_j)\, dE' \quad (40)$$

where the subscript α labels the target fragment type, $S_\alpha(E)$ is the stopping power, and E_α and E_j are in units of MeV.

The particle fields of the projectiles and target fragments determine the level and type of radiological damage at the end point of interest. The relationship between the fields and the cellular response is now considered within the Katz cellular track model.

The ion-kill term now contains a projectile term (Cucinotta et al. 1991b) and a target fragment term as

$$(\sigma F) = \sigma_j(E_j)\phi_j(x, E_j) + \sum_\alpha \int_0^\infty dE_\alpha \phi_\alpha(x, E_\alpha; E_j)\sigma_\alpha(E_\alpha) \quad (41)$$

while the corresponding gamma-kill dose becomes

$$D_\gamma = [1 - P_j(E_j)]S_j(E_j)\phi_j(x, E_j) + \sum_\alpha \int_0^\infty dE_\alpha [1 - P_\alpha(E_\alpha)]S_\alpha(E_\alpha)\phi_\alpha(x, E_\alpha; E_j) \quad (42)$$

Use of equations (40) and (41) allows one to define an effective cross section as

$$\sigma_j^*(E_j) = \sigma_j(E_j) + \sum_\alpha \int_0^\infty dE_\alpha \frac{\sigma_\alpha(E_\alpha)}{S_\alpha(E_\alpha)} \int_{E_\alpha}^\infty dE' \frac{d\Sigma_{\alpha j}(E', E_j)}{dE'} \quad (43)$$

The first term of equation (43) is caused by the direct ionization of the media by the passing ion of type j. The second term results from target fragments produced in the media.

The Katz (Waligorski et al. 1987) cellular parameters for survival of C3H10T½ that are fit to the experiments of Yang et al. (1989) as given in table I are used to evaluate target fragment contributions according to equations (42) and (43). General agreement with the measured RBE values (Waligorski et al. 1987) was found by using these parameter sets. The single-particle inactivation cross section neglecting the target fragmentation of equation (43) is shown in figure 4 for cell death as a function of the energy (MeV/amu) of the passing proton. The target fragmentation contribution (the second term of eq. (43)) has been evaluated and is also shown in figure 4. For protons, the effect of the target fragments (dashed line, the second term of eq. (43)) dominates over the proton direct ionization (dotted line) at high energy. For high-LET particles (low energy), the direct ionization dominates and target fragmentation effects become negligible. The effects of target fragments on the gamma-kill dose (eq. 42) are small (Cucinotta et al. 1991b) and are neglected here. The effective cross section is now used to study the repair capability of the cell for target-fragment-induced lesions. We have calculated the immediate and delayed plating responses, including and neglecting target fragment contributions, and show the results in figure 5.

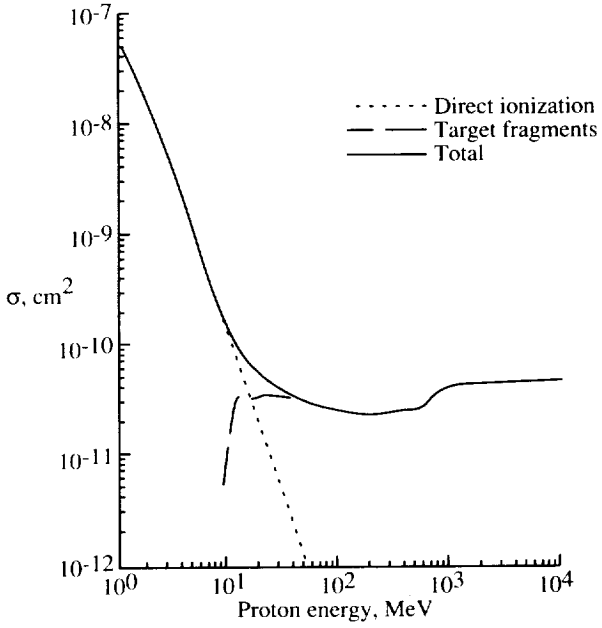


Figure 4. Katz cross section for protons in C3H10T½ cells.

Results for 10 MeV proton exposures are shown in figure 5(a). The response curves are characteristic of X-ray exposures, and target fragments play a small role at this energy. Exposures at 50 MeV and 100 MeV clearly display target fragment effects (figs. 5(b) and 5(c)) but are beyond our ability to measure in biological experiments. Target fragment effects are quite large at 1000 MeV as shown in figure 5(d). A clearly reduced capability of the cell to repair fragment-induced lesions is shown. When target fragments are neglected, the response curves are nearly those expected for X-ray exposures.

Concluding Remarks

The multilesion track structure model described herein agrees well with the available experimental data for C3H10T½ cells. The lack of repair capability of the cell for target-fragment-induced damage by high-energy protons is predicted by the model. We must await further experiments to confirm these predictions. As experimental data become available, this model should be easily adapted to exposure effects due to continuous heavy ion exposure in space. It is doubtful that any other method will be found for estimation of space exposure risk since space exposure conditions cannot be duplicated completely in a laboratory environment.

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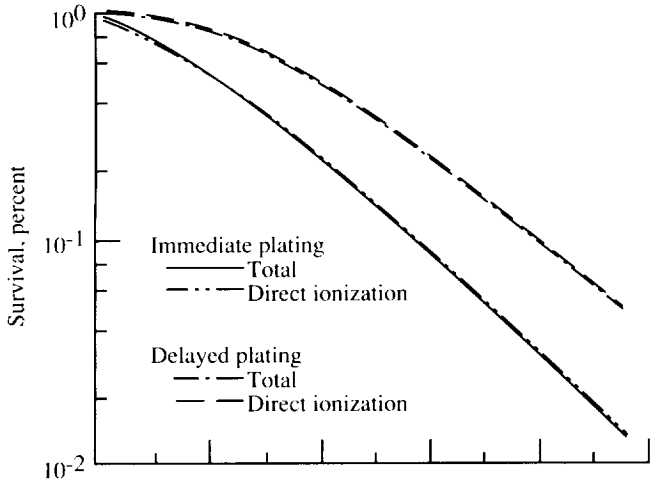
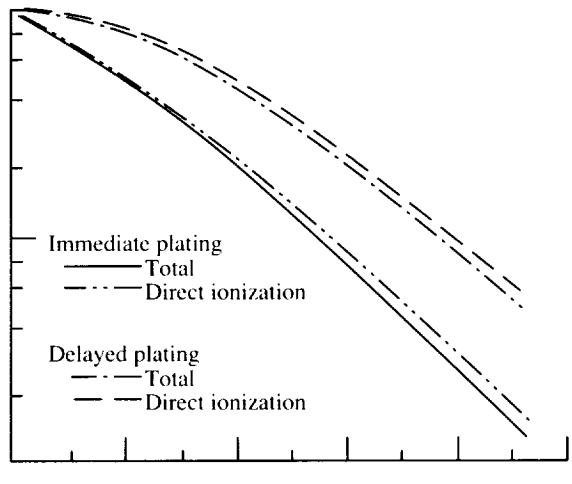
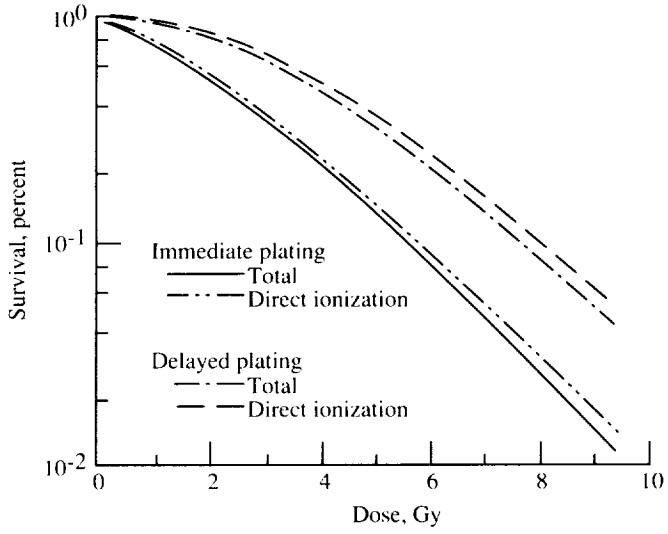


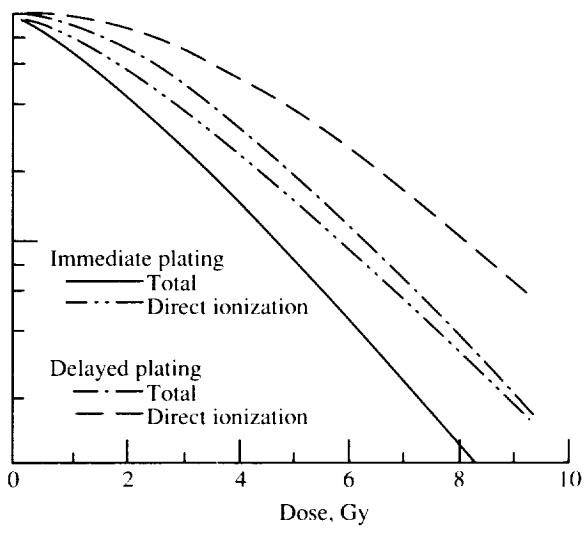
(a) $E = 10$ MeV.



(b) $E = 50$ MeV.



(c) $E = 100$ MeV.



(d) $E = 1000$ MeV.

Figure 5. Survival curves for proton exposure of C3H10T½ cells.

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A multilesion cell kinetic model is derived, and radiation kinetic coefficients are related to the Katz track structure model. The repair-related coefficients are determined from the delayed plating experiments of Yang et al. for the C3H10T½ cell system. The model agrees well with the X-ray and heavy ion experiments of Yang et al. for the immediate plating, delaying plating, and fractionated exposure protocols employed by Yang. A study is made of the effects of target fragments in energetic proton exposures and of the repair-deficient target-fragment-induced lesions.

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